

Liver Cancer: Much to Learn about a Neglected Cancer

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Etiologies of Liver Cancer

- Infection: chronic viral hepatitis (HBV, HCV ad HDV)
- Toxin: alcohol, aflatoxin B1, aristolochic acid, other toxins
- Metabolic disease: NASH
- Autoimmune liver disease: autoimmune hepatitis, primary biliary cirrhosis
- Genetic disease: hemochromatosis, Wilson disease, alpha 1-antitrypsin, acute porphyria
- Cirrhosis of other causes

Cancer Statistics of USA and Worldwide

Cancer Type	~ New Cases	~ Deaths
Breast	255,180	41,070
Lung	222,500	155,870
Prostate	161,360	26,730
Colon	135,430	50,260
Melanoma	87,110	9,730
Bladder	79,030	16,870
Lymphoma	72,240	20,140
Kidney	63,990	14,400
Leukemia	62,130	24,500
Uterus	61,380	10,920
Thyroid	56,870	2,010
Pancreas	53,670	43,090
Liver	40,710	28,920

71%

Cancer Type	~ New Cases	~ Deaths
Lung	1,824,701	1,589,800
Breast	1,676,633	521,817
Colon	1,360,602	693,881
Prostate	1,111,689	307,471
Stomach	951,594	723,027
Liver	782,451	745,517
Cervix	527,624	265,653
Esophagus	455,784	400,156
Bladder	429,793	-

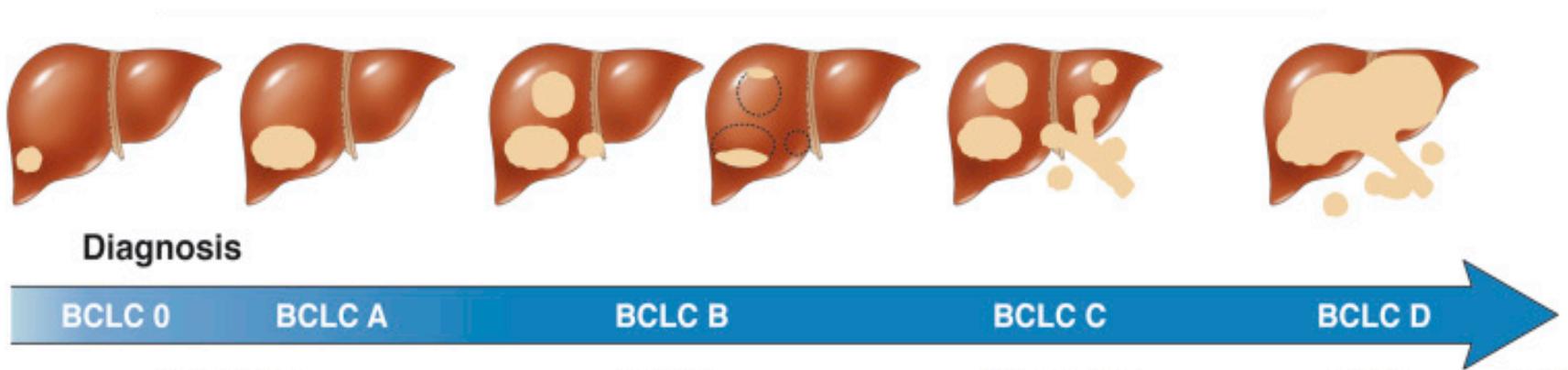
WHO/IARC 2014

95%

Surveillance for Liver Cancer

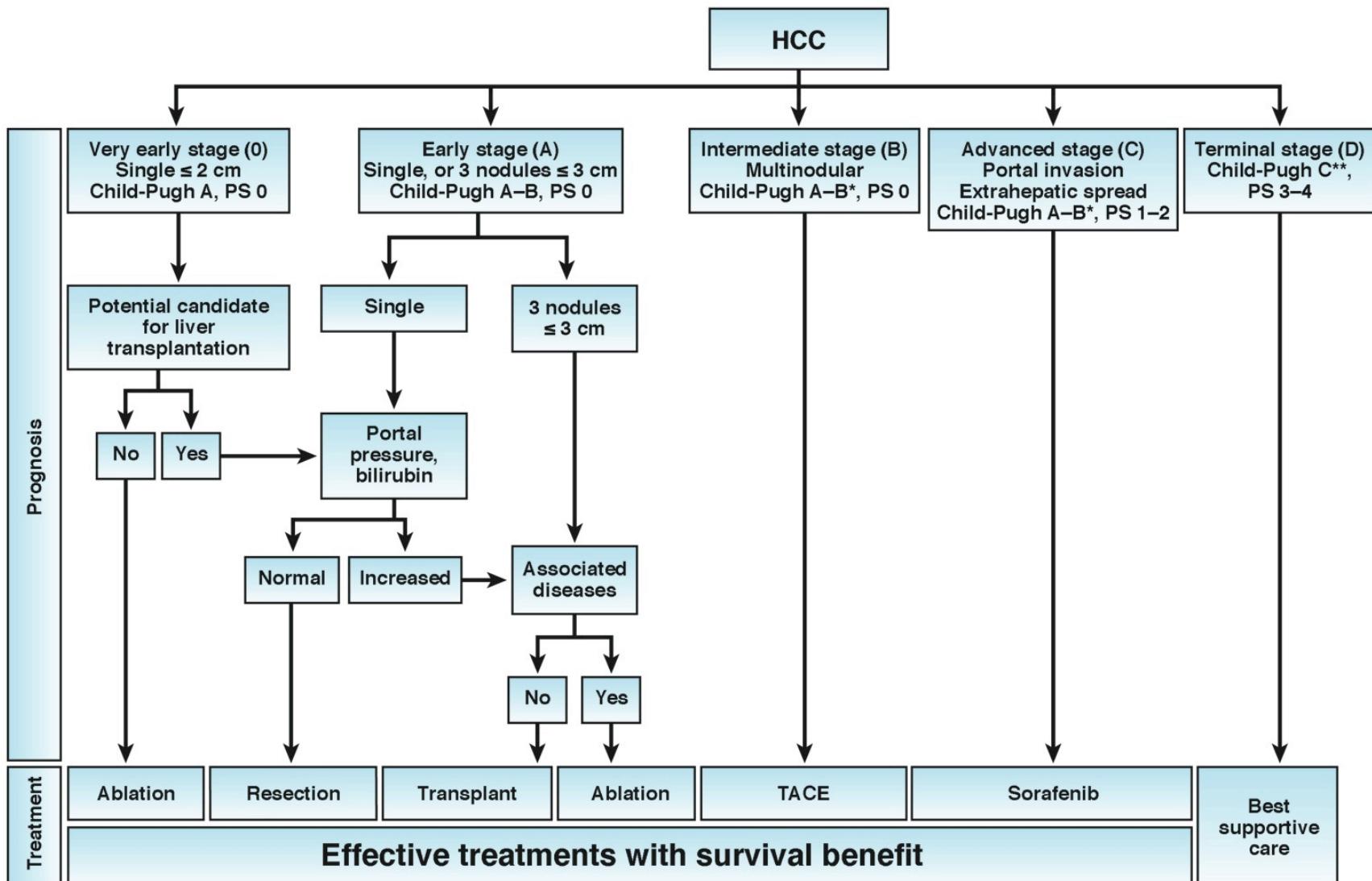
- **Chronic viral hepatitis with cirrhosis**
 - **Cirrhosis of any etiology**
 - **Race and family history**
-
- **Ultrasound every 6-12 months**
 - **AFP not officially recommended but still used by many**
 - **Other tests: des- γ -carboxy prothrombin, L3 fraction of AFP, and other biomarkers**

Liver Cancer Staging and Treatment Strategy



Bruix, Reig and Sherman Gastroenterology 2016

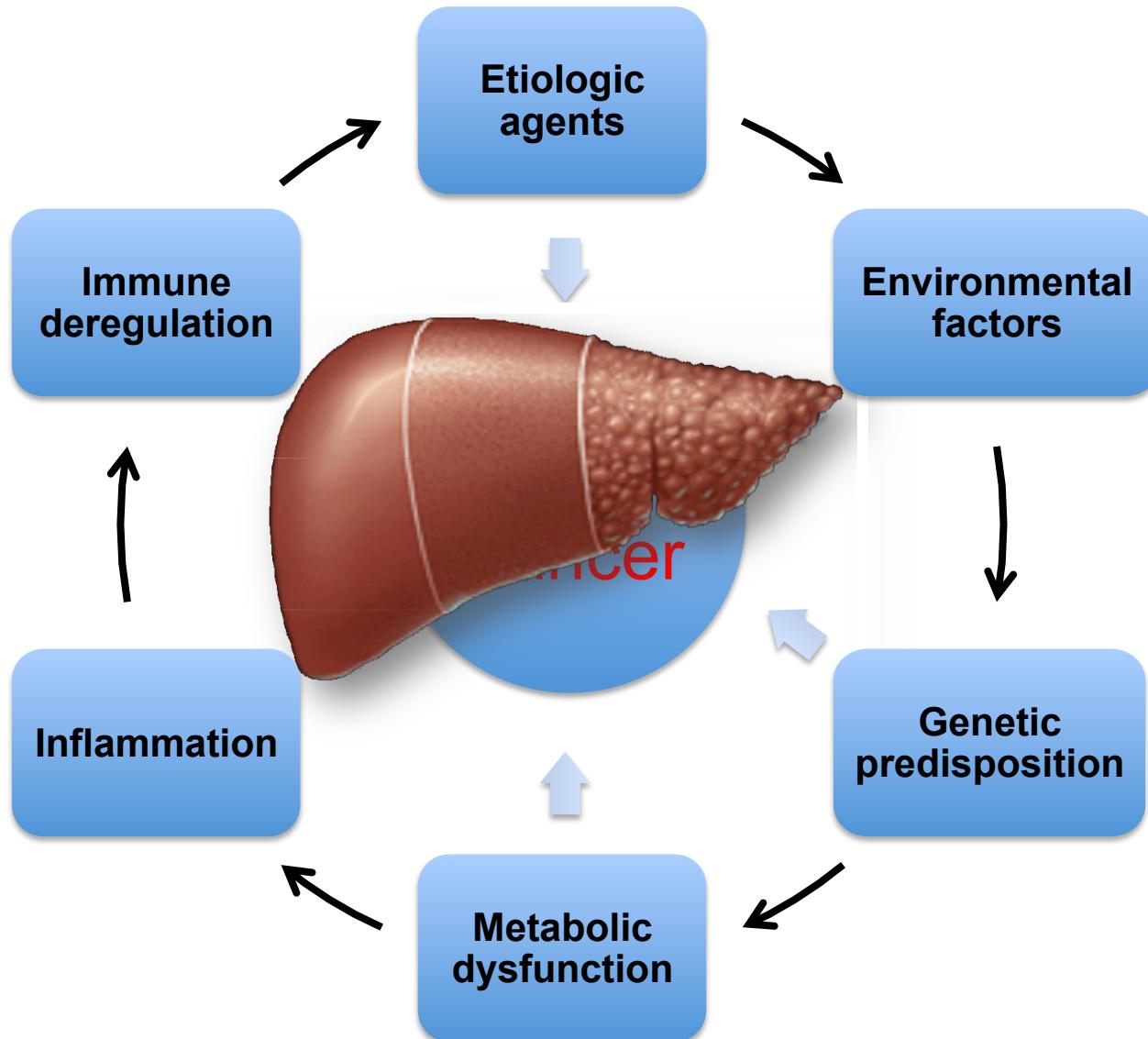
Liver Cancer Treatment Algorithm



*Note that Child-Pugh classification is not sensitive to accurately identify those patients with advanced liver failure that would deserve liver transplant consideration.

**Patients with end stage cirrhosis due to heavily impaired liver function (Child-Pugh C or earlier stages with predictors of poor prognosis, high MELD score) should be considered for liver transplantation. In them, HCC may become a contraindication if exceeding the enrollment criteria.

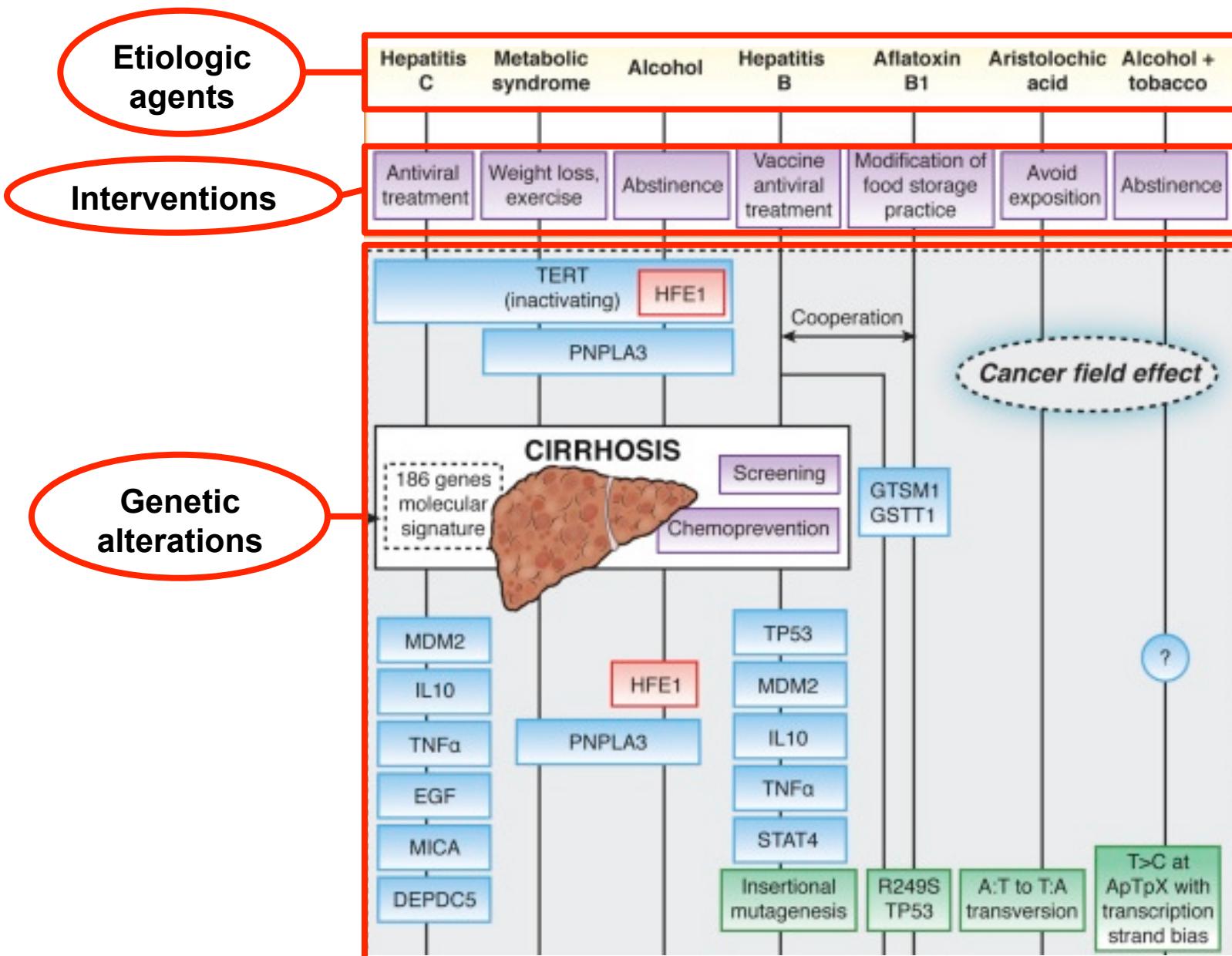
Pathogenesis of Liver Cancer



Genetics of Liver Cancer: “Driver Genes”

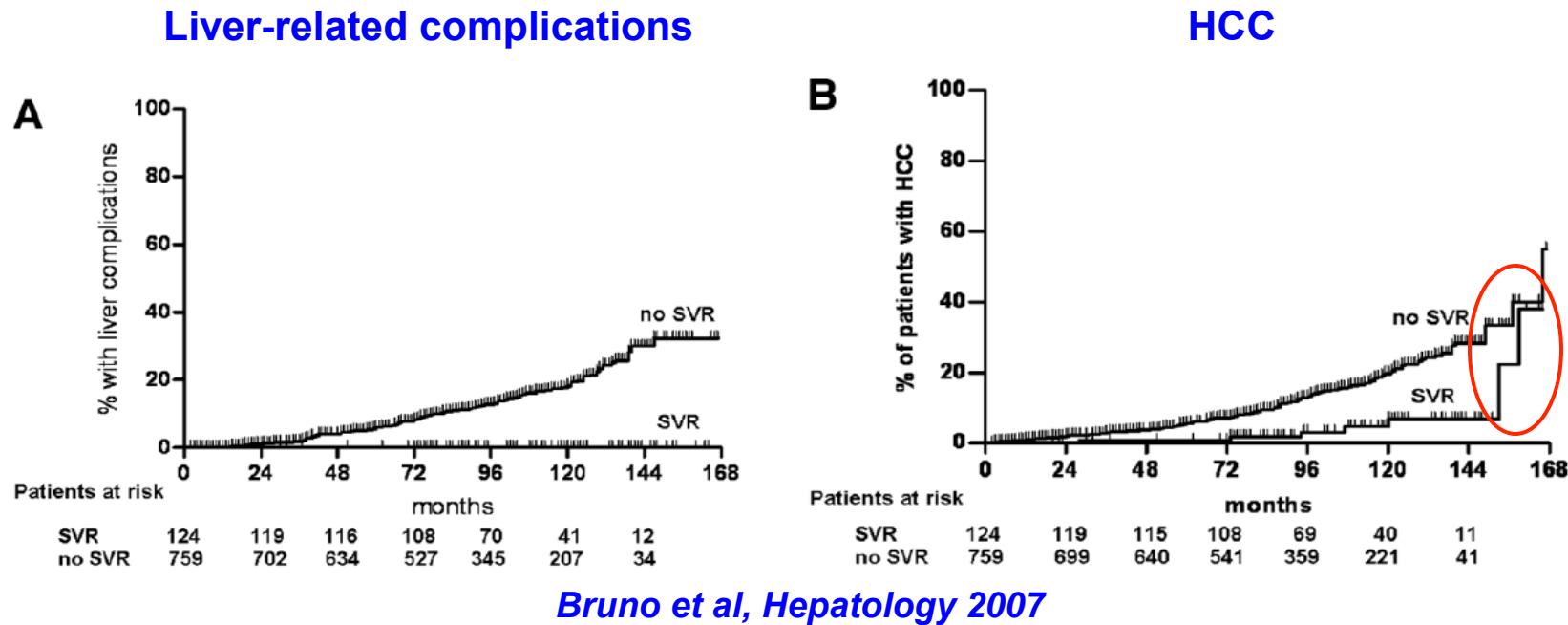
- **Telomerase**
- **p53**
- **WNT/β-catenin**
- **Myc**
- **PI3K/AKT/MTOR**
- **RAS/RAF/MAPK**
- **NRF2**

Genetic Landscape and Biomarkers of HCC



Risk of HCC in HCV Patients with Sustained Virological Response?

- HCV patients with SVR have a reduced risk of HCC



Veldt et al, Annals Int Med 2007; Morgan et al, Hepatology 2010; Backus et al, Clin Gastroenterol Hepatol 2011; Chou et al, AHRQ 2012; Van der Meer et al, JAMA 2012; McCombs et al, JAMA 2014.

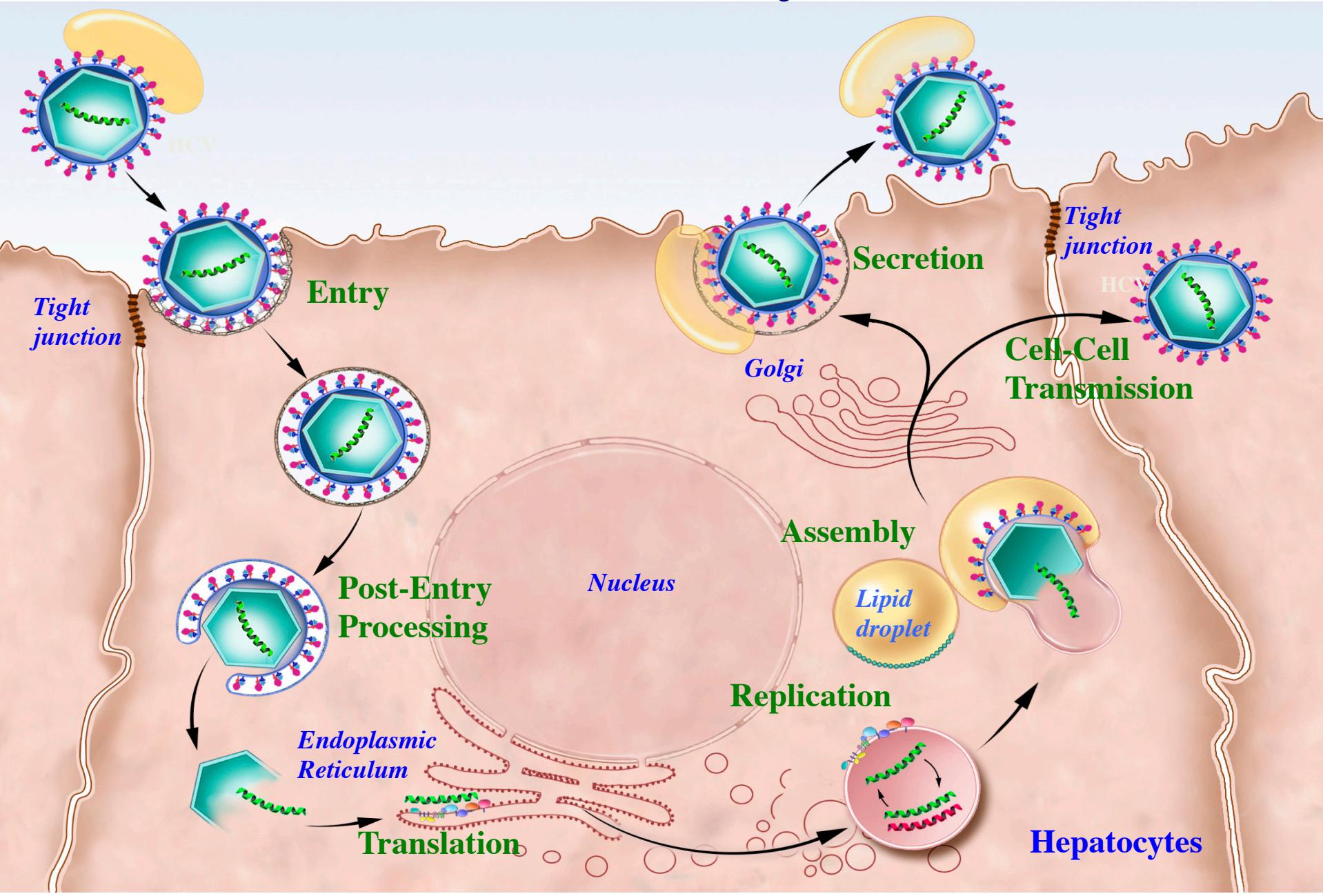
- HCV patients with SVR are still at risk for HCC; cirrhosis

Tokita et al, J Gastro Hepatol 2005; Tanaka et al, World J Gastro 2007; Kobayashi et al, Liver Int 2007

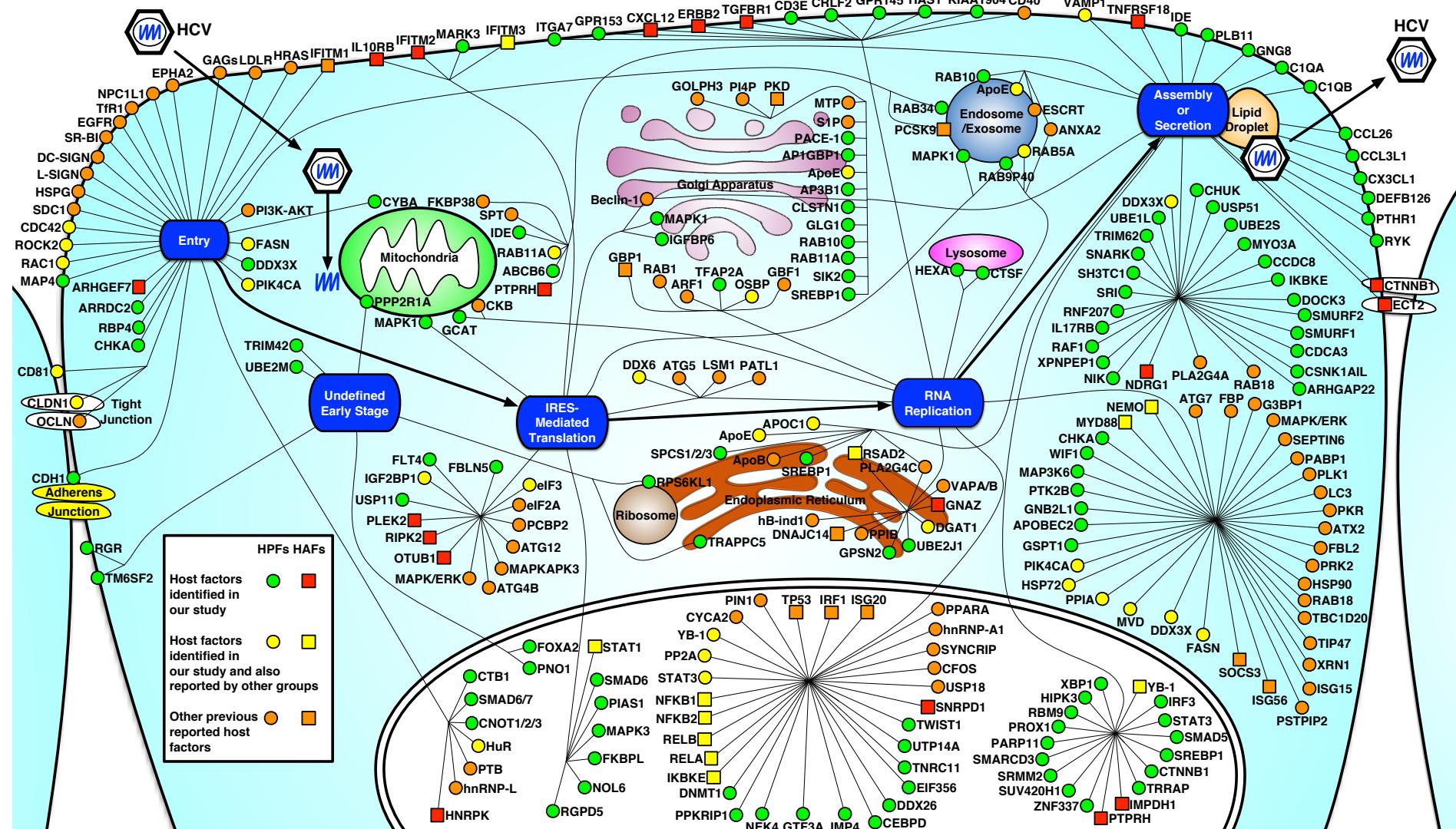
Virus and Cancer

- **Virus's purpose in “life” is to propagate in its infected host**
- **Virus has evolved to exploit and modulate host functions for propagation**
- **Virus has evolved multiple mechanisms to counteract host antiviral response**
- **Viral-induced disease is predominantly a result of host response to viral infection**
- **Viral-associated carcinogenesis is a secondary para-phenomenon and unintended by-product of viral infection**

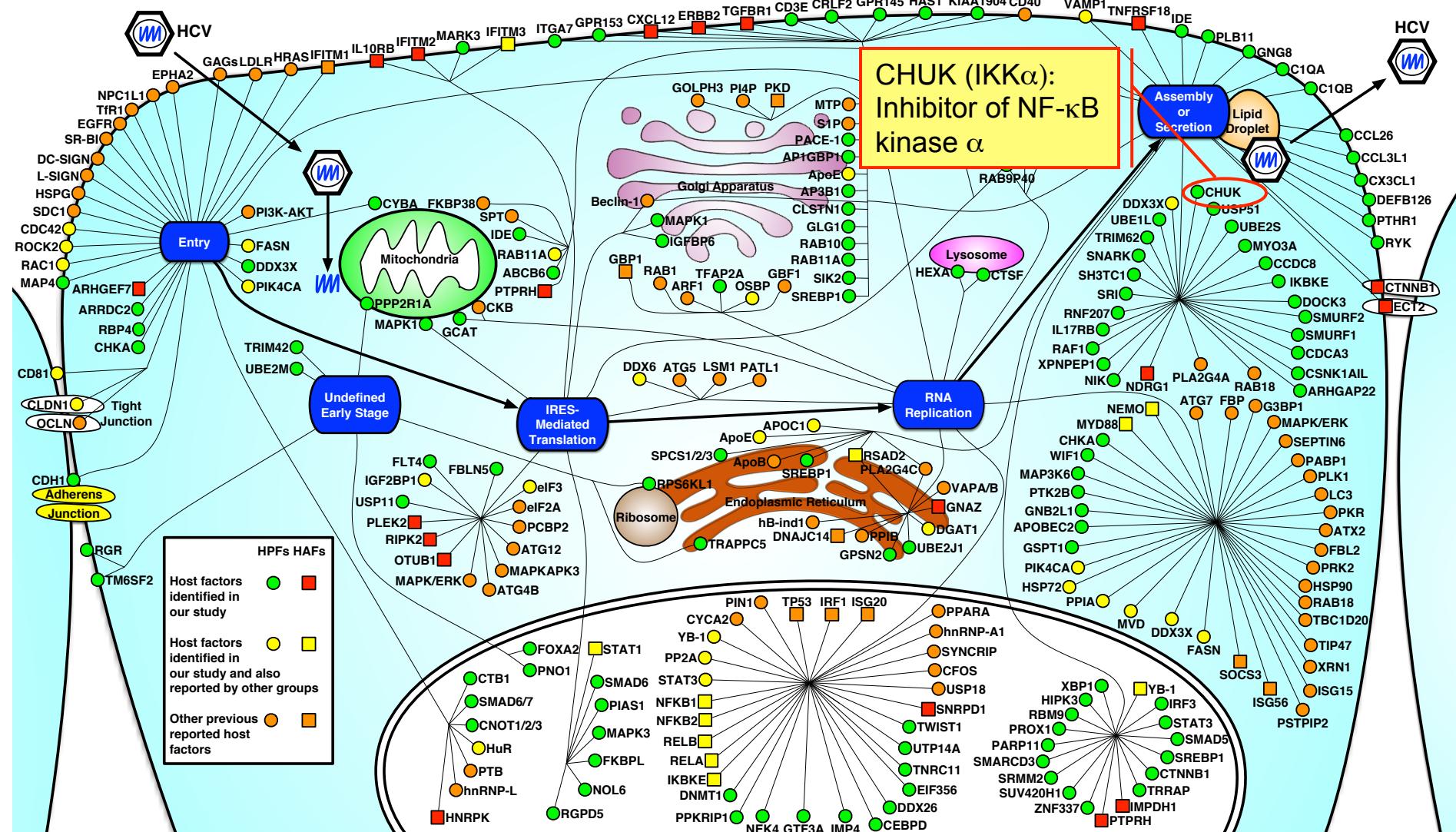
HCV Life Cycle



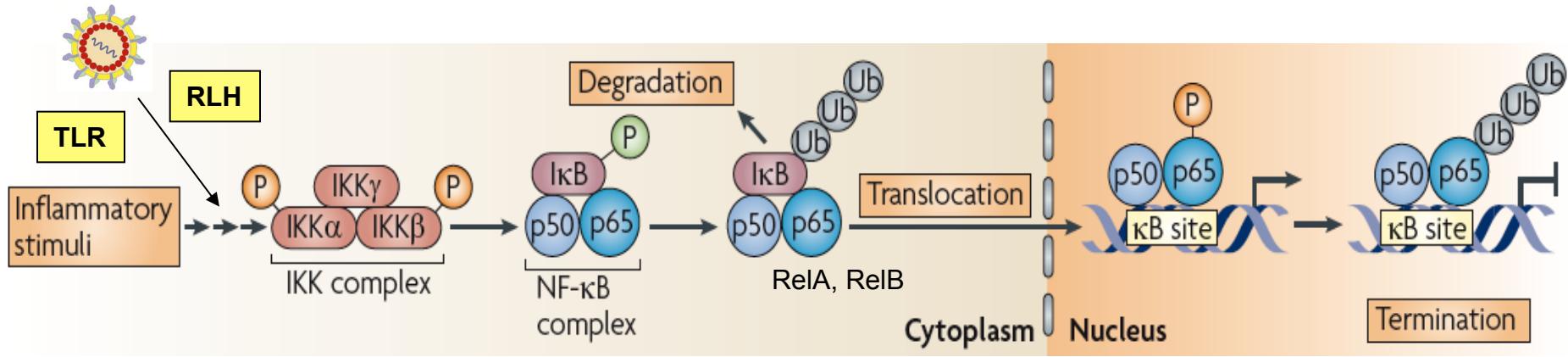
Systems Biology of Host Factors in HCV Life Cycle



Systems Biology of Host Factors in HCV Life Cycle



NF-κB Pathway

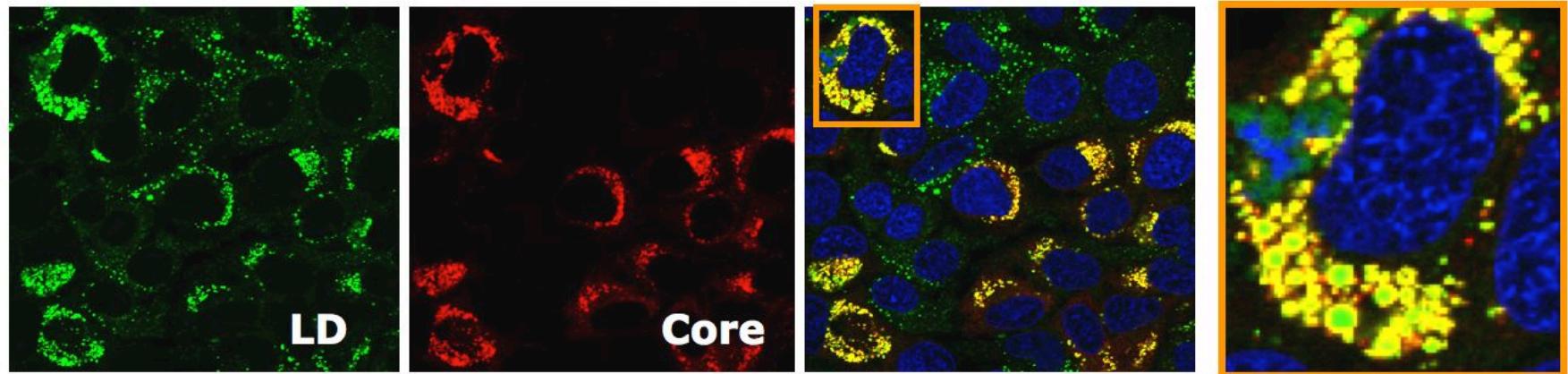


Gosh & Hayden Nat Rev Immunol 2008

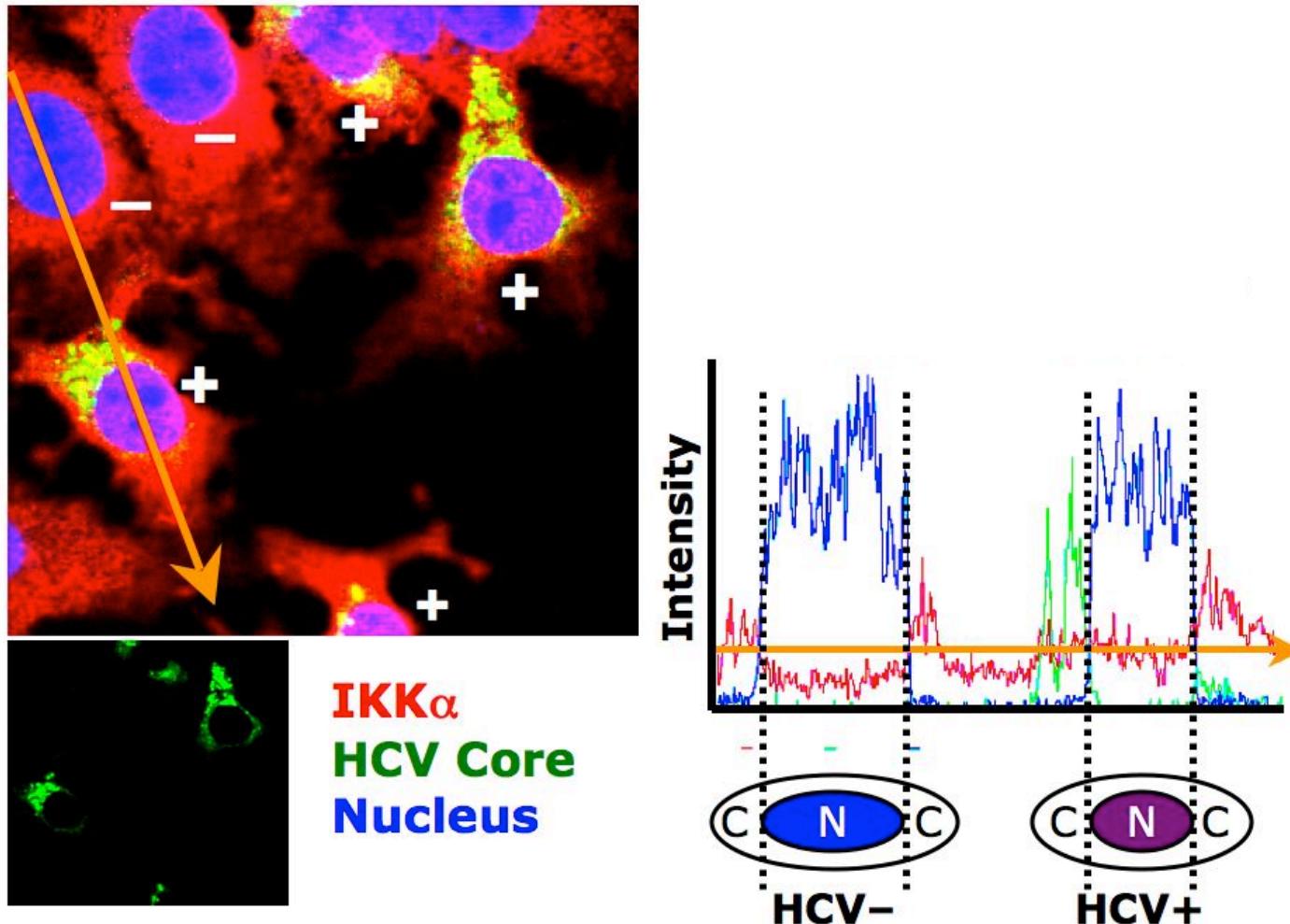
- Antiviral response (IRF3, IRF7, IRF9): induction of IFN pathway
- IKK β & IKK γ (NEMO) in canonical NF-κB activation
- IKK α (CHUK) in non-canonical pathway (NF-κB2)

Lipid Droplet Formation and IKK α

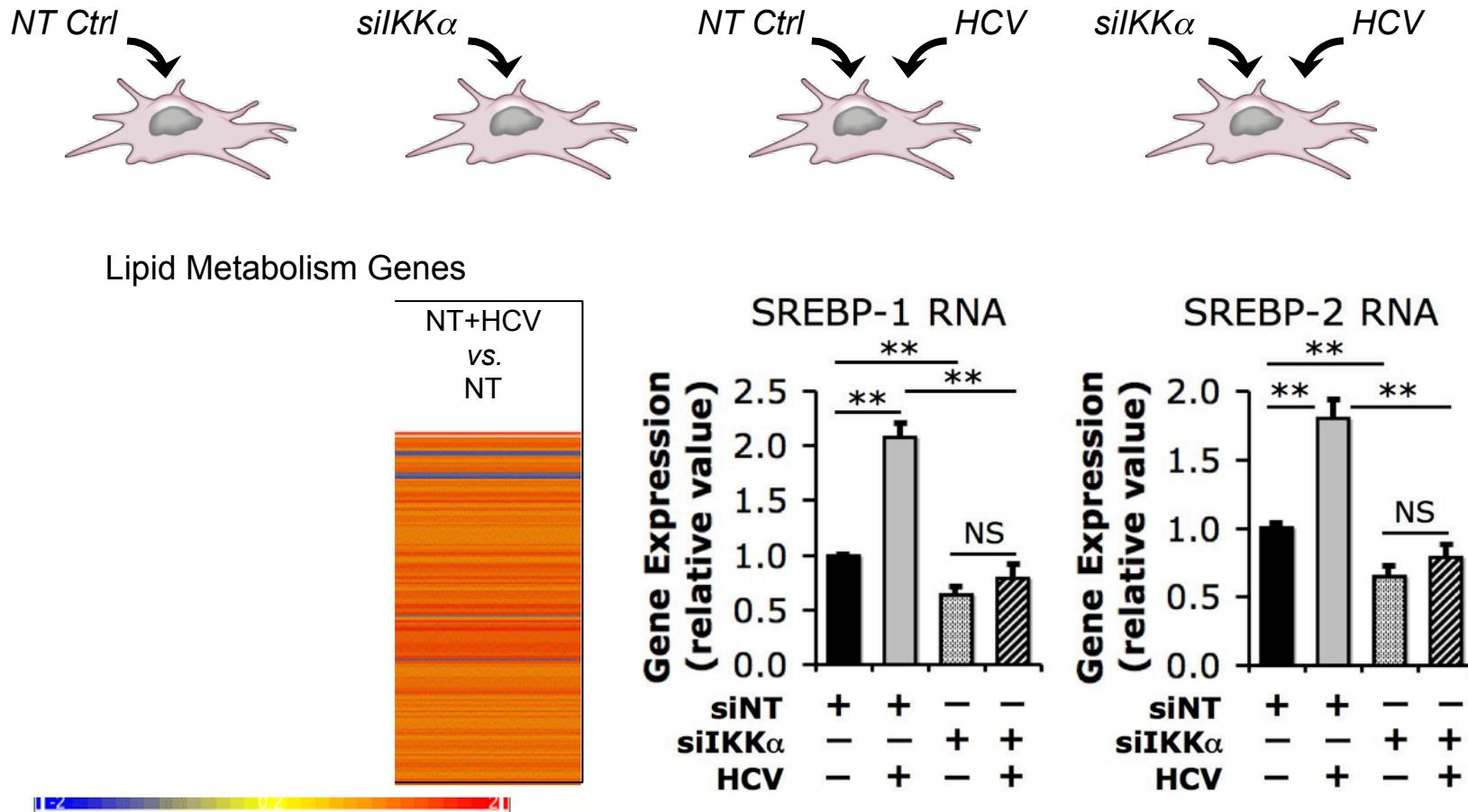
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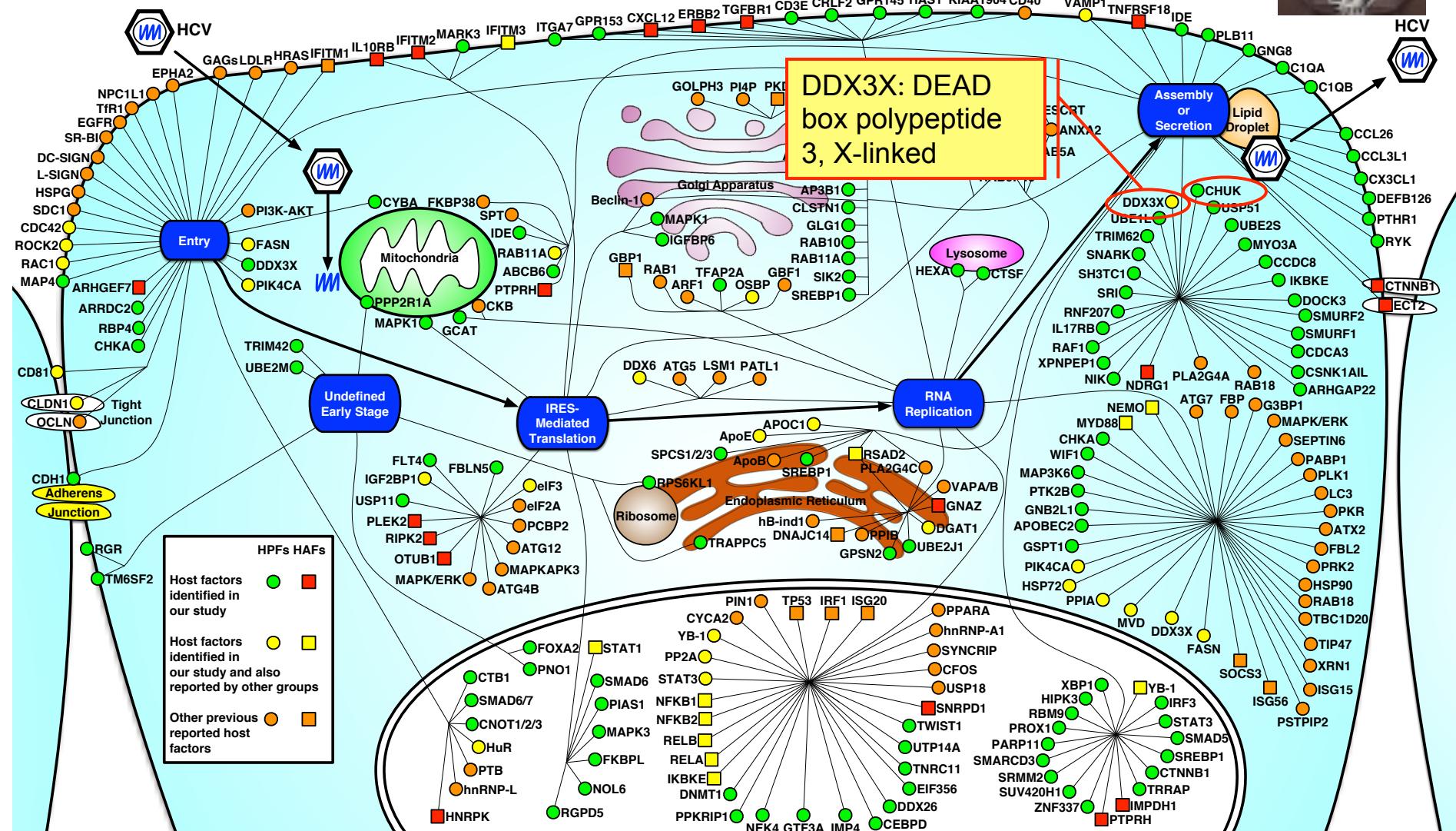
Nuclear Localization of IKK α in HCV Infected Cells

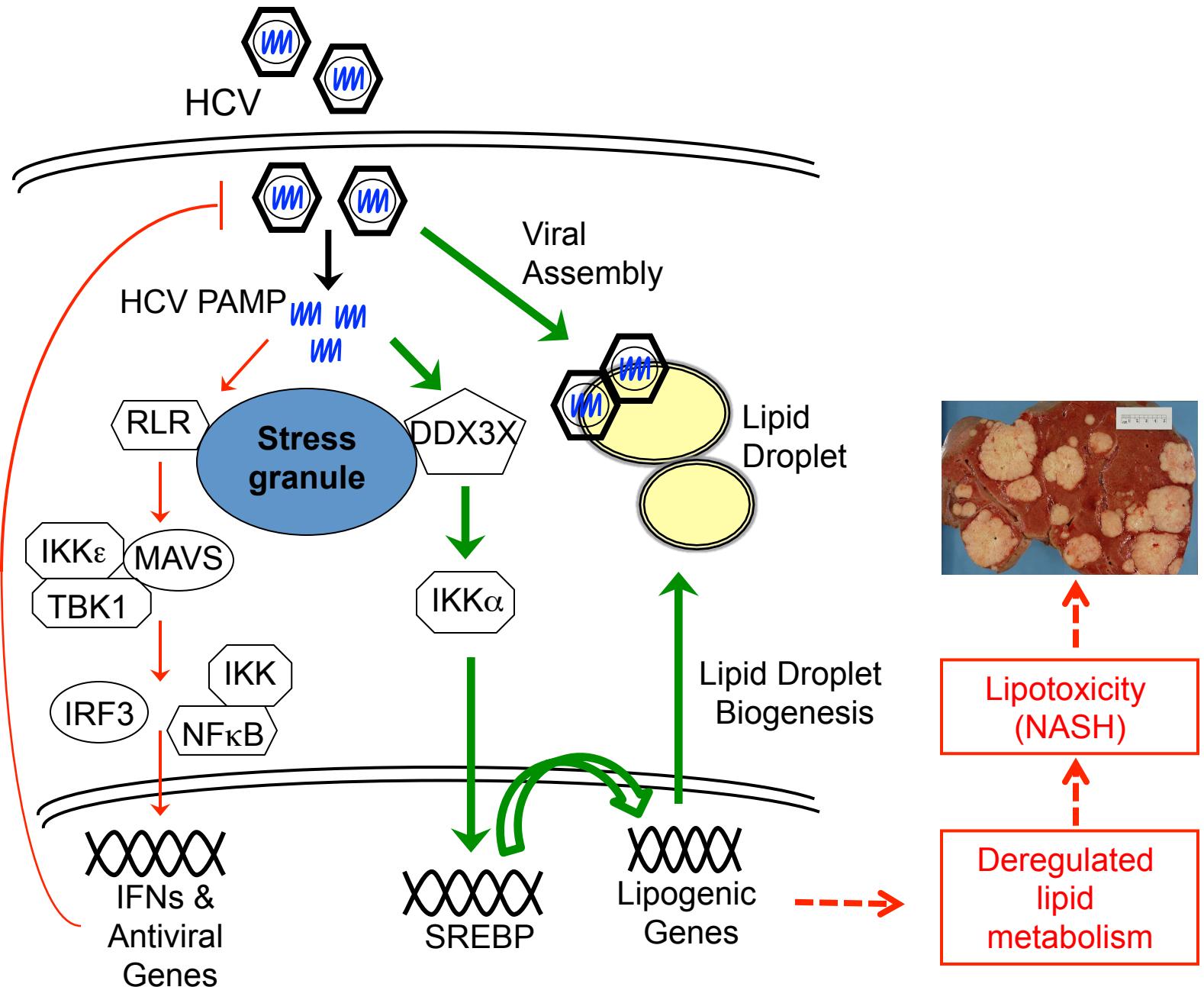


Role of IKK α in HCV Infection by Microarray Gene Expression Analysis

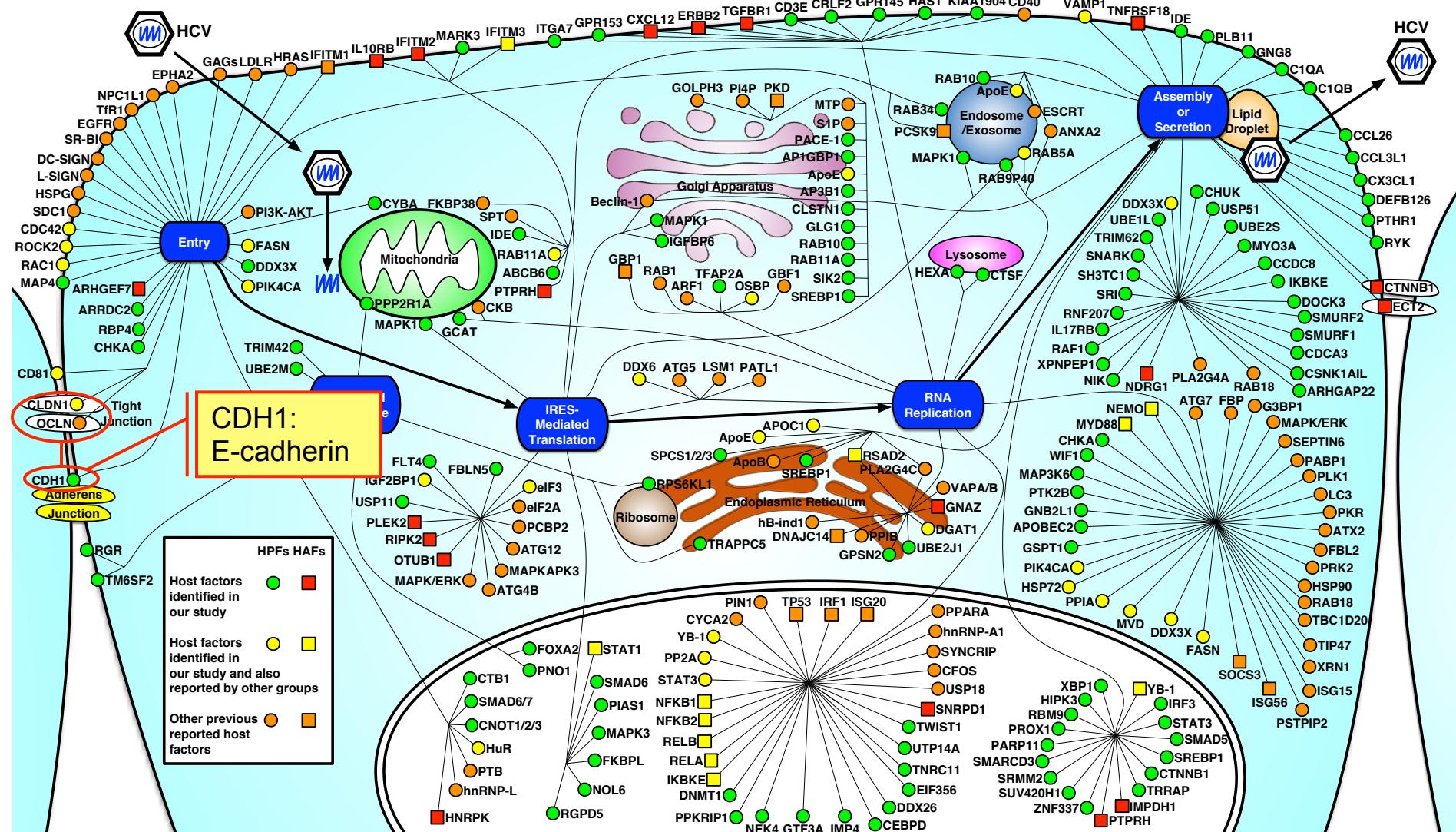


Systems Biology of Host Factors in HCV Life Cycle





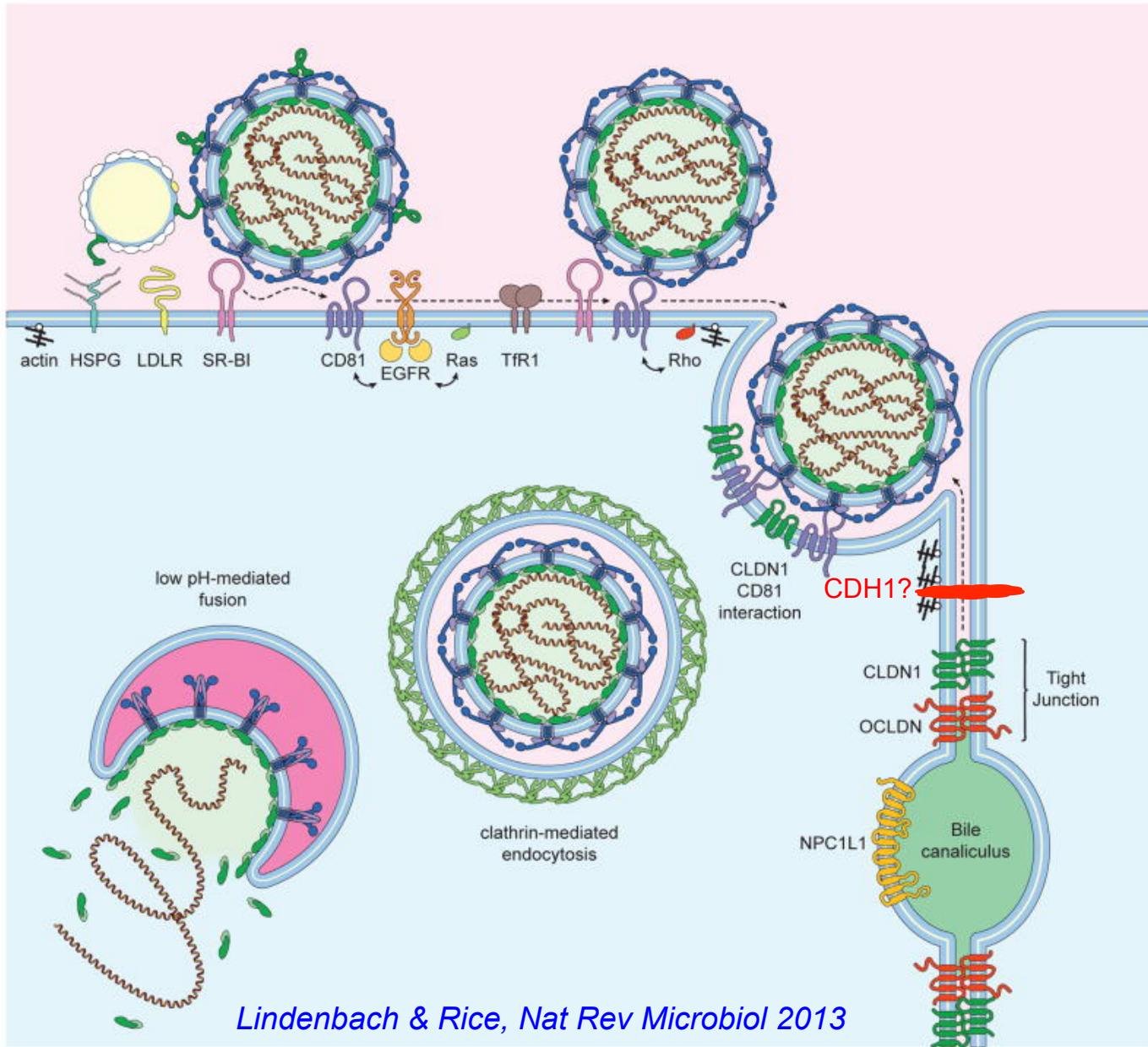
Systems Biology of Host Factors in HCV Life Cycle



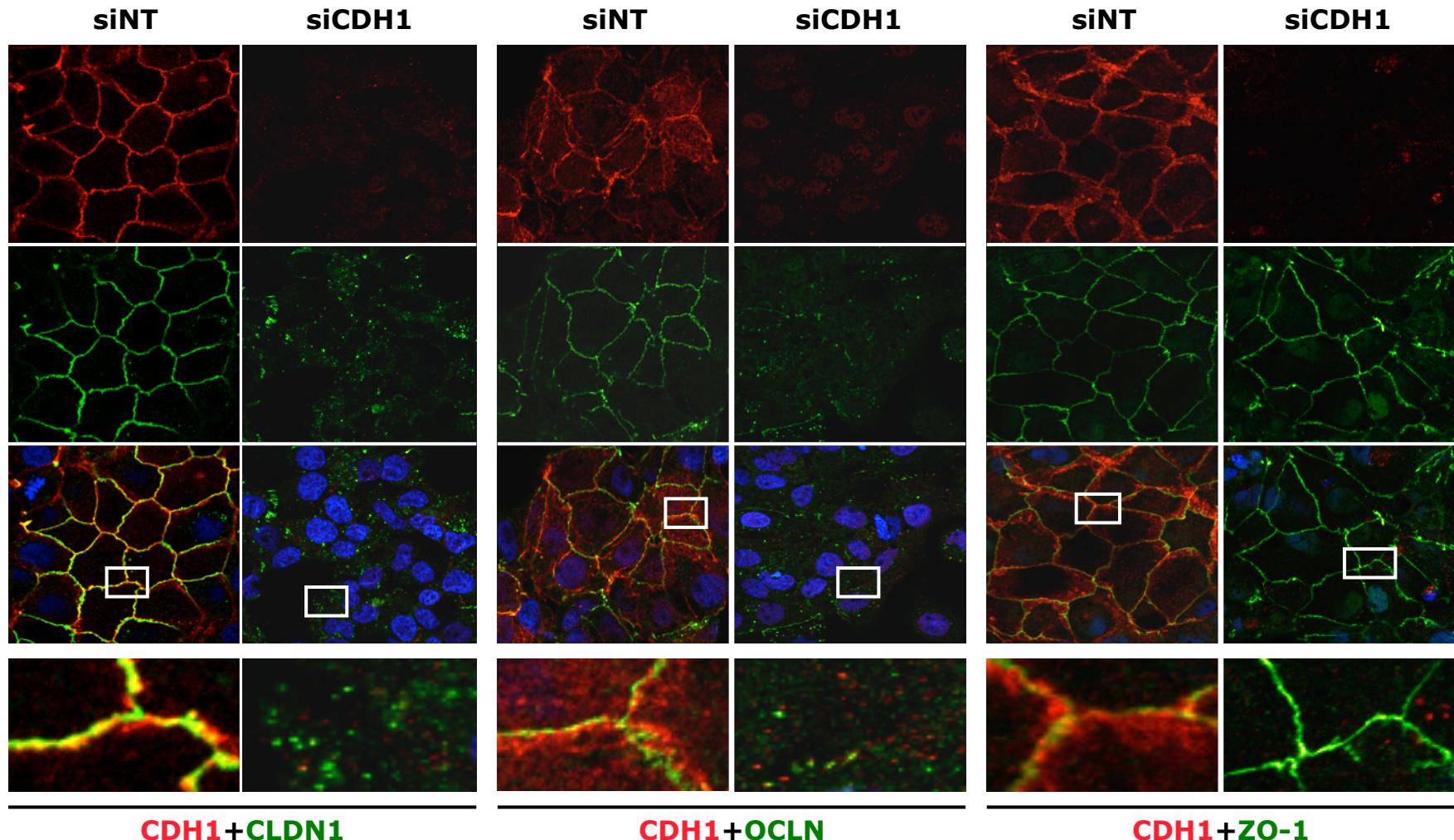
E-cadherin

- **Adherens junctions: cadherins and nectins**
- **Cell polarity and organogenesis**
- **Malignant transformation: epithelial-to-mesenchymal transition**
- **Signal transduction: catenins**
- **Target of microbial invasion**

HCV Entry Factors

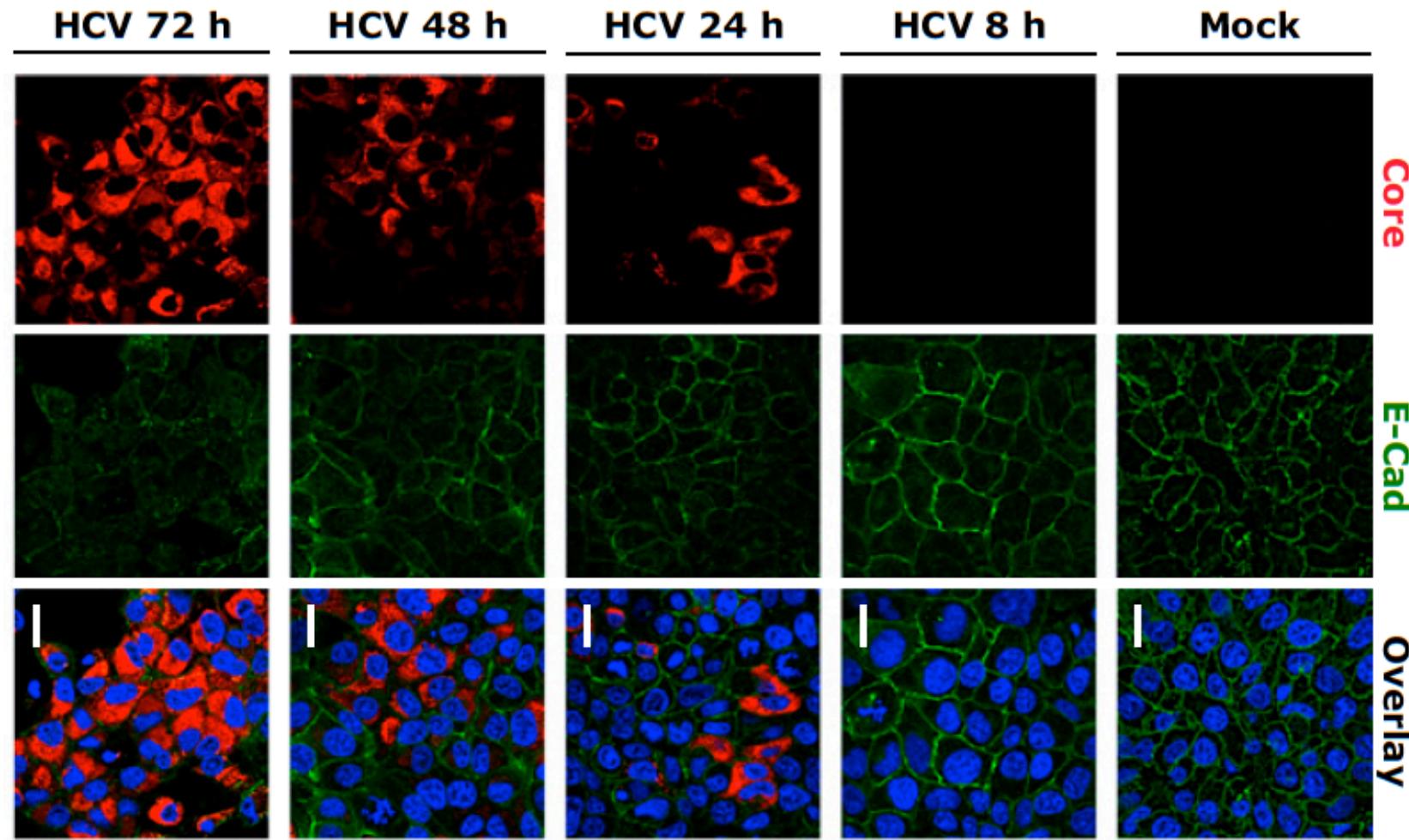


Interaction of E-cadherin with HCV Entry Factors

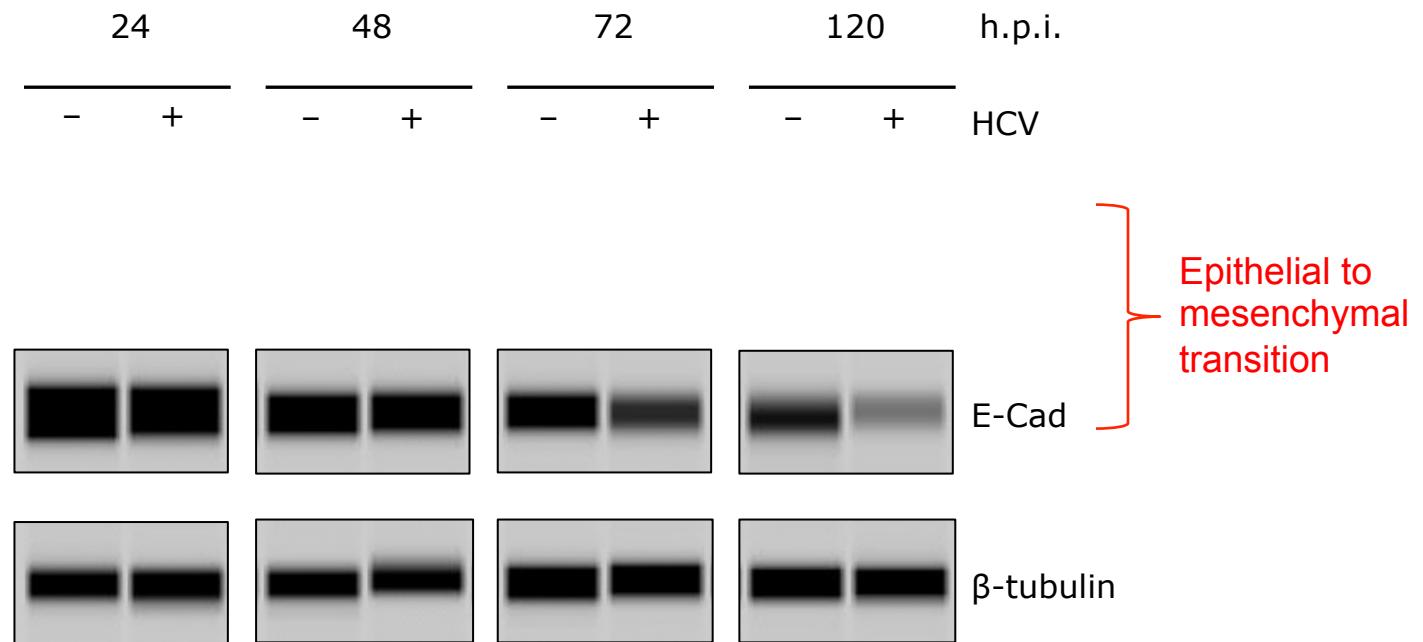


- E-cadherin regulates localization of claudin 1 and occludin on cell surface

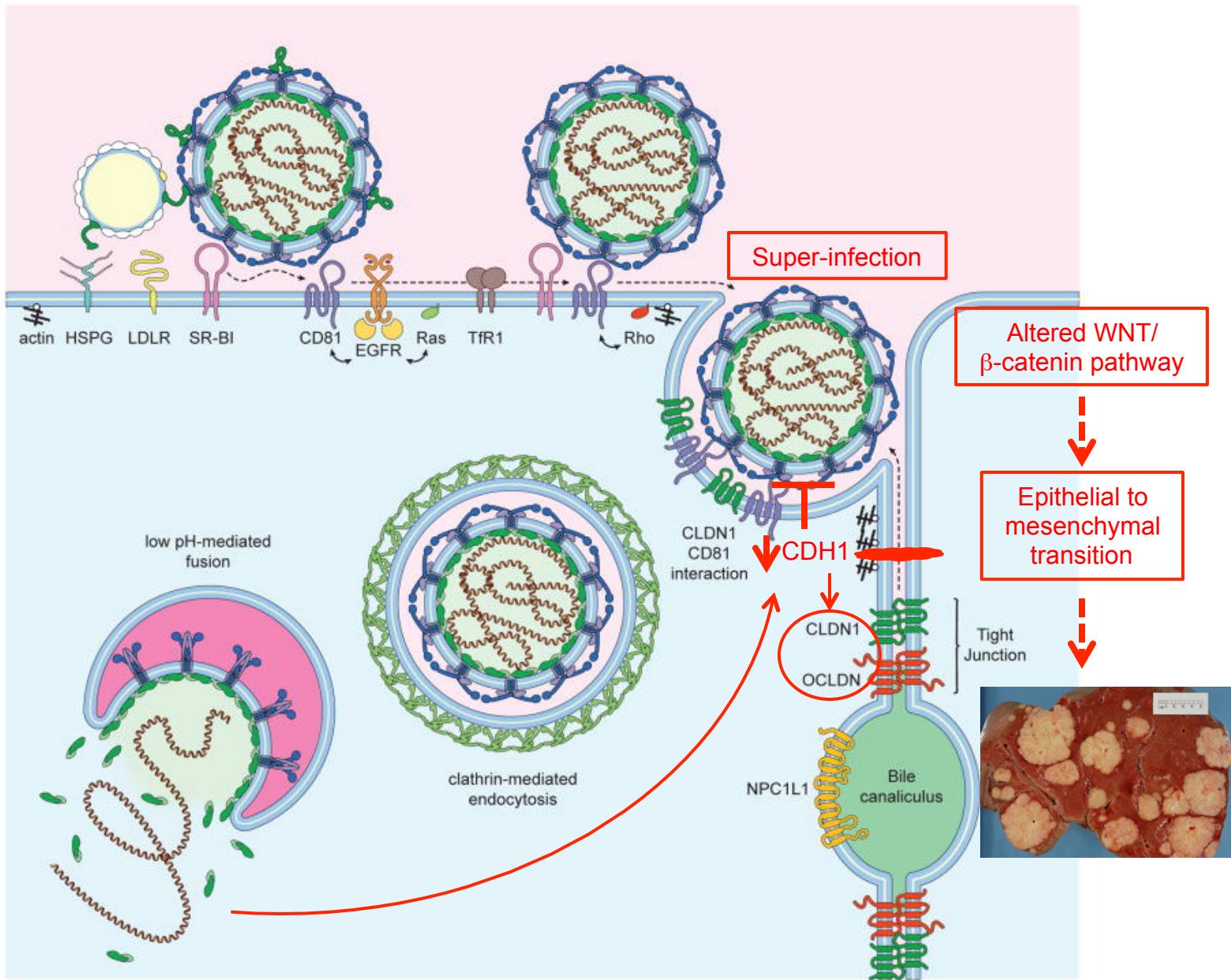
HCV Causes the Loss of E-cadherin Expression



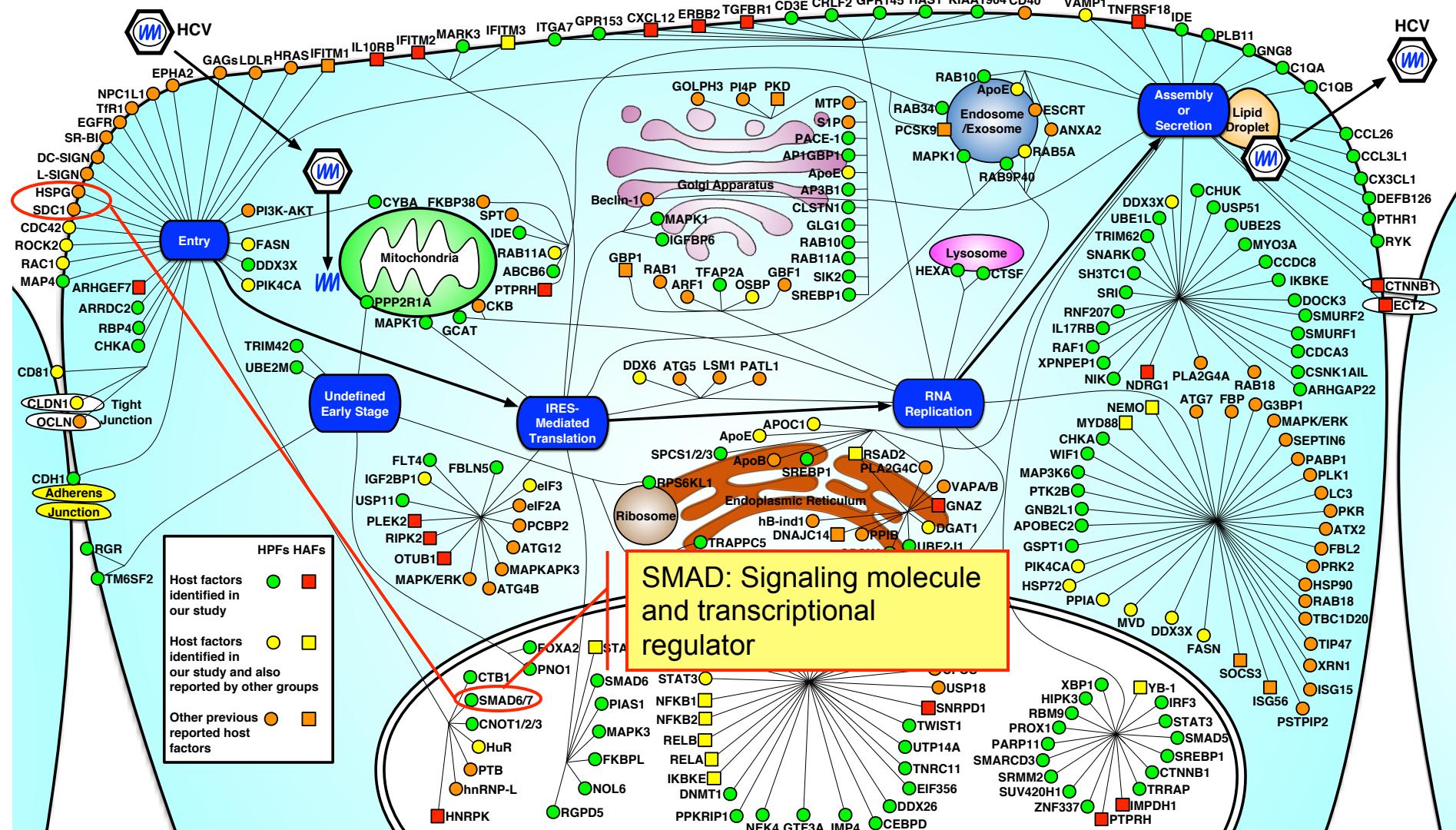
HCV down-regulates E-cadherin Expression



HCV & E-cadherin



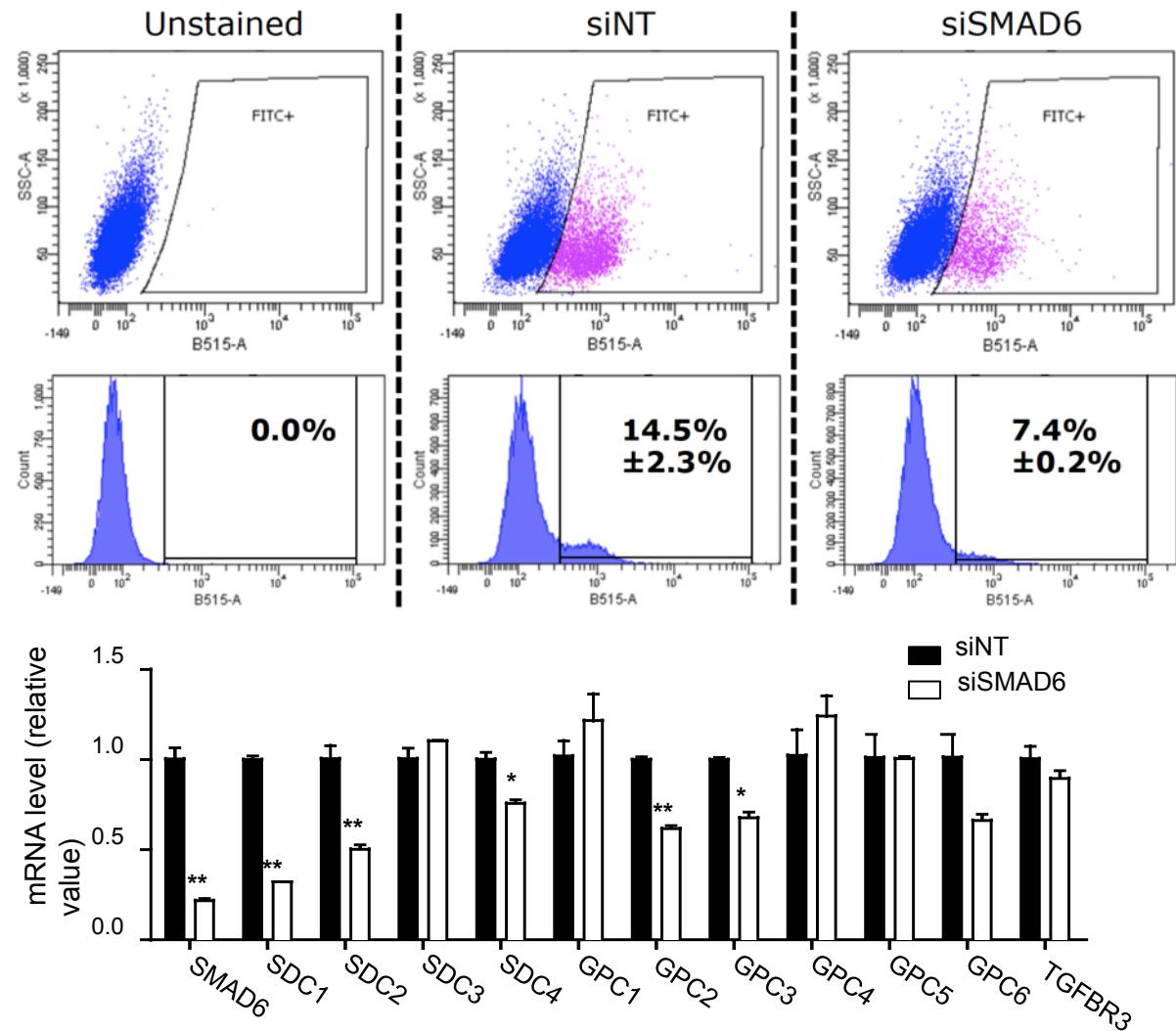
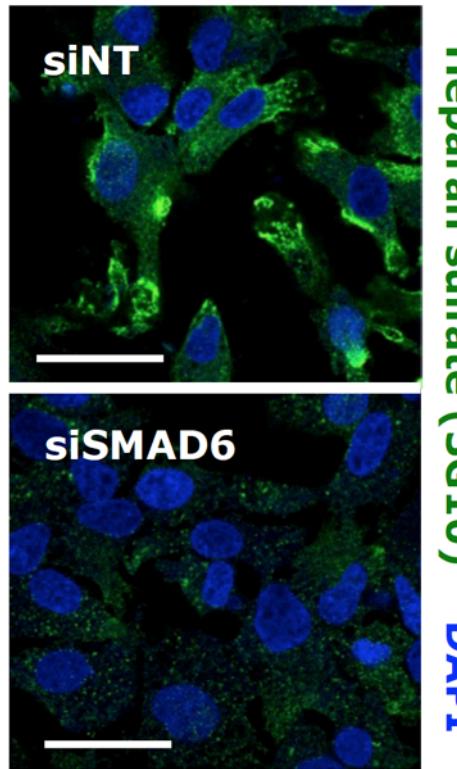
Systems Biology of Host Factors in HCV Life Cycle



SMAD6

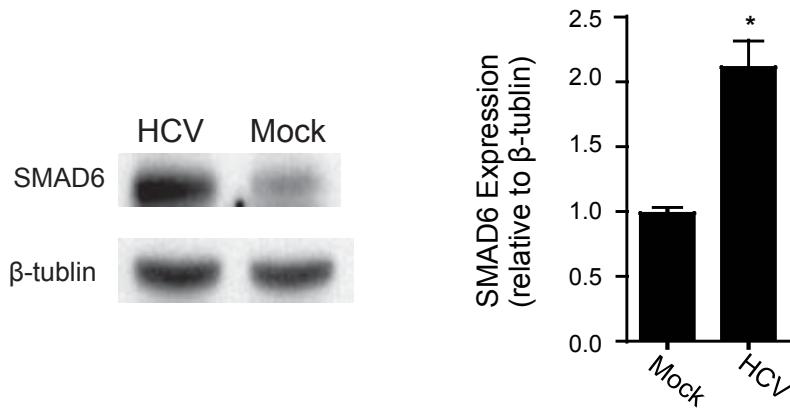
- **SMAD family signal transducers:** mediate TGF- β family signaling
- **SMAD6 and 7 are I-SMADs:** induced by TGF- β signaling as feedback inhibitors by blocking R-SMADs functions
- Direct transcriptional function, independent of R-SMADS

SMAD6 Controls Heparan Sulfate Expression on Cell Surface

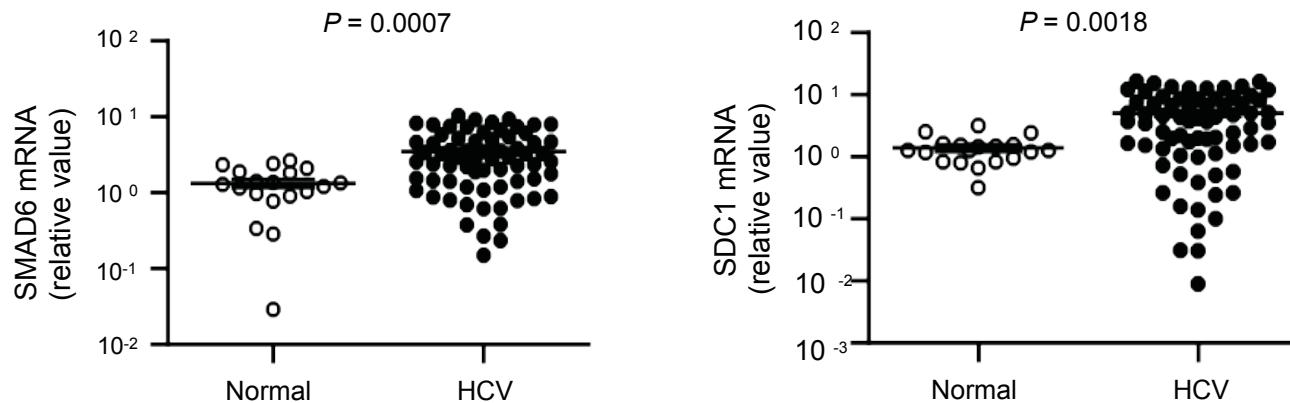


SMAD6 Expression in HCV-Infected Cells

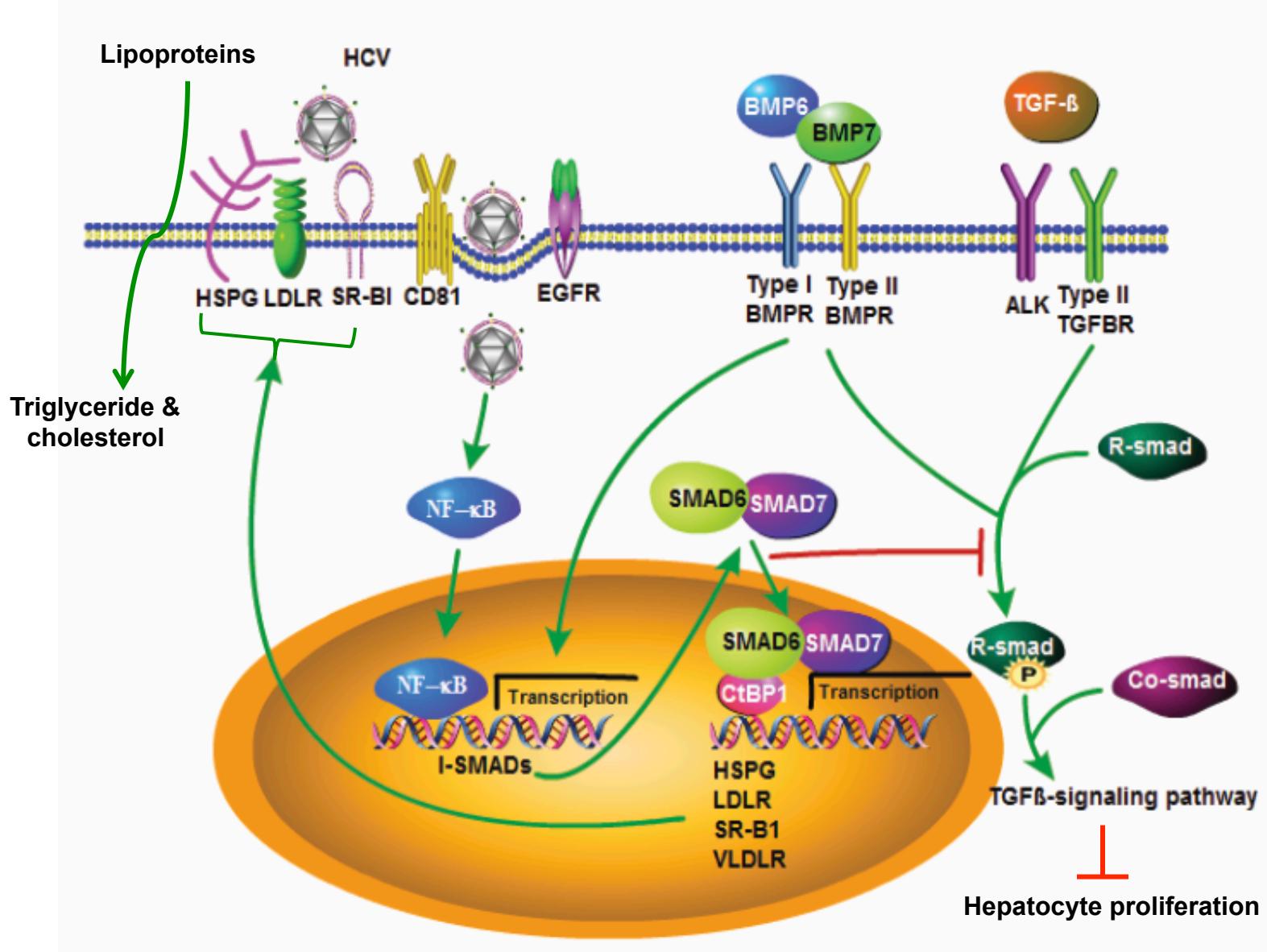
Primary human hepatocytes



Liver biopsies



HCV Infection, I-SMAD and Lipid Metabolism



HCV Infection and HCC

- **Mapping of critical pathways in HCV-cell interactions generates novel insight into the molecular mechanisms of HCV-associated hepatocarcinogenesis**
- **HCV infection establishes a premalignant phenotype that predisposes to HCC development**
- **This premalignant phenotype can be integrated into the genetic landscape of established HCC**
- **HCC is a heterogeneous cancer, each type defined by its etiology, and is ideal for precision medicine regarding prevention and therapy**

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Q. Frank Li



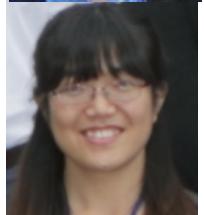
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Sidd
Krishnamurthy



Helen Cha



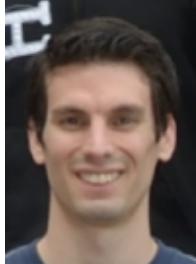
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Catherine Sodroski



Stephan Chiu



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